Future Directions In Transplantation

Highlights from the American Transplant Congress

Washington State Convention and Trade Center, Seattle, Washington, USA
21 - 25 May 2005

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SEATTLE 2005

The waterside city of Seattle, named after the Native American leader, Chief Sealth, is one of America's newest and most attractive metropolises. Before the rise of the high-tech economy, Seattle's time as a thriving timber port contributed little to its national image. This changed in the 1990s, when the "Emerald City" became the corporate headquarters of iconic companies such as Starbucks® and Microsoft®.

The timing of this commercial boom coincided with the advent of grunge music. The meteoric rise of seminal bands such as Nirvana and Pearl Jam established Seattle as this genre's nominal birthplace.

From 21-25 May, leading scientists and clinicians from all four corners of the globe converged in Seattle, Washington state, to attend the 2005 *American Transplant Congress (ATC)*. This e-report summarises the key proceedings from the meeting, including oral presentations, posters, and presenter interviews.

Roche

THE BIG INTERVIEW

Christopher Dudley [CLICK ON NAME FOR ABSTRACT], ***Southmead Hospital, Bristol, UK*** presented a two-year follow-up of the 'Creeping Creatinine' CsA withdrawal study. *Future Directions* caught up with Dr Dudley to discover his thoughts on these latest results and on transplantation research in general.

FD: *What are the major issues in the transplant environment?*

CD: *"In the past, post-transplant clinical management has focused on reducing acute rejection and improving one year graft survival rates. Generally speaking, these two issues have now been addressed and new challenges have evolved. The current shortage of organ donors is a particular concern and, in some countries, the number of transplant surgeons is also insufficient. In terms of clinical outcomes, chronic allograft nephropathy (CAN) remains problematic, while more consideration is being afforded to quality-of-life parameters such as rehabilitation and cosmetic side effects."*

FD: *Are any of these issues currently being addressed?*

CD: *"There is a huge amount of work going on. Tailored immunosuppression is certainly sensible, although of course, you need to have proof-of-concept from running controlled trials. Quality-of-life concerns have prompted extensive research into patient-friendly immunosuppression, with CNI- or steroid-sparing regimens becoming increasingly popular.*

"However, some interesting work has not been followed-up, such as the Flechner CNI-free study, and I'm worried about the lack of convincing data regarding combinations which are both CNI- and steroid-free."

FD: *How would you like to see transplant management evolving?*

CD: *"More studies should focus on reducing CAN, as it doesn't appear that CNI-free regimens completely address this issue. Reperfusion injury should also be investigated further, in terms of maximising organ quality at the time of transplantation."*

FD: *What was the rationale for the Creeping Creatinine study?*

CD: *"We've seen far too many studies which rely on short-term follow-up, so in our trial, we were very keen to add a long-term element. Although an improvement in graft survival for an additional year is worthwhile, it is particularly interesting to see what happens two, three or four years later."*

CONTINUES ON NEXT PAGE

THE BIG INTERVIEW continued

BACK

FD: *How would you summarise the results?*

CD: *"I had hoped to see more substantial improvements in graft survival, but it was a relatively small study and was perhaps not powered to show that. I was also hoping for more dramatic differences in graft function, but since a large proportion of patients in the control arm reported a treatment violation, these data were not quite as expected.*

"However, the good news is that we can conclude that CsA withdrawal after MMF substitution is safe, with no late acute rejection events, and that this substitution leads to equivalent patient and graft survival. It also appears that any improvement in renal function occurs early and is sustained over three years. In addition, the difference in two-year creatinine is statistically significant in patients in the MMF group who remain CNI-free, when compared with patients who continue CNIs in the CsA group.

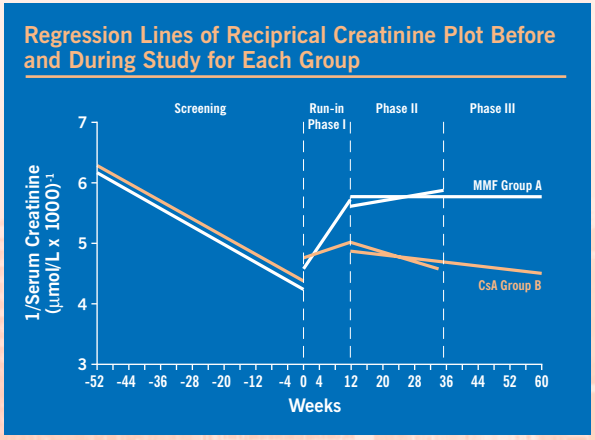
"In the future, it might be interesting to perform a six-month or one-year withdrawal study in a stable patient population, along the same lines as the five-year CNI-sparing study by Abramowicz et al which is due to be published shortly. There may also be a benefit in comparing MMF with rapamycin."

FD: *Have the study results changed your practice?*

CD: *"We've been influenced from an early stage, and have continued to withdraw CNIs in patients with chronic allograft dysfunction often without performing a transplant biopsy. We therefore have a large population of patients on MMF and prednisolone. Our own clinical experience is that the vast majority of patients do benefit from this approach, and that we tend to see this benefit relatively quickly."*

FD: *Are there any plans to continue the study?*

CD: *"Our plan is to complete four-years of follow-up to provide five-year data from baseline. We appreciate that patient numbers may have dwindled by then, but we will endeavour to address that."*



Late-Breaking

The increasing use of the Rapa/FK combination – evidence for worse renal allograft survival

When compared to MMF/FK, Rapa/FK results in significantly inferior clinical outcomes

Herwig-Ulf Meier-Kriesche [CLICK ON NAME FOR ABSTRACT], *University of Florida, Gainesvile, Florida, USA* presented a retrospective analysis of 44,915 adult renal transplant recipients. Here, Professor Meier-Kriesche summarised the study during his presentation.

"Tacrolimus (FK) is perceived to be less nephrotoxic than cyclosporine (CsA), and as a result, several of us have switched to a Rapa/FK discharge combination. However, now that sufficient follow-up data are available from the national transplant registry, we decided to compare the outcomes from this combination with those of other discharge regimens, especially the most commonly prescribed combination of mycophenolate mofetil (MMF) and FK.

"Unadjusted univariate analysis showed a statistically significantly difference in overall graft survival between MMF/FK and Rapa/FK after three years (85.9% vs 80.3%, p<0.001). In higher risk patients, this difference was even more pronounced (74.5% vs 57.5%, p<0.001).

"Multivariate data, corrected for confounding variables, confirm that, compared to MMF/FK, graft survival for Rapa/FK is significantly worse. These data show that Rapa/FK is associated with around a 50% increase in graft loss. MMF/FK also showed similar superiority in patient survival, death-censored graft survival, overall graft survival in living recipients, and overall graft survival in expanded criteria donor (ECD) recipients.

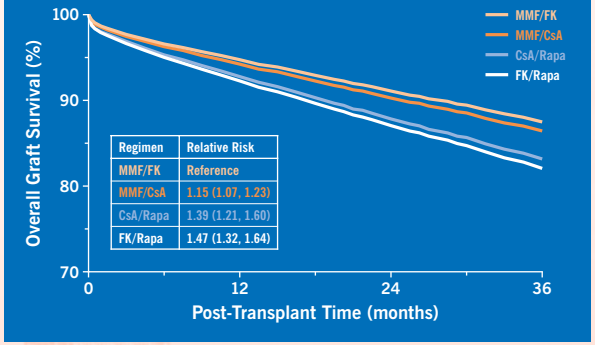
"It is also interesting to note that the two regimens have similar acute rejection rates during the first year. However, as the resulting graft survival rates were clearly very different, it shows that these two parameters have no clinical correlation.

"We can conclude that when compared to MMF/FK, Rapa/FK is associated with significantly worse graft survival in all subgroups of patients, and particularly in patients with high risk grafts which might show earlier susceptibility to nephrotoxic insults. The magnitude of this difference is similar, if not bigger, than the previously described effect of CsA/Rapa.

"There are obviously caveats to any type of retrospective analysis. We clearly have no drug exposure data, and were limited to an intention-to-treat analysis. However, there are now two prospective, randomised trials that mirror these data."

H. Meier-Kriesche

Multivariate Cox Proportional Hazard Model for Overall Graft Loss



Poster Session – Kidney: Post-Transplant Complications

Management of diarrhoea in renal transplant recipients: the DIDACT study

Diarrhoea remission can be achieved without changing the immunosuppressive regimen

B. D. Maes [CLICK ON NAME FOR ABSTRACT], *Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium* presented an open, prospective, non-randomised, multicentre study of 108 renal transplant recipients with severe diarrhoea.

The aim of the study was to collect data on the diagnosis of severe diarrhoea, defined in a standardised manner, with the aim of minimising changes to patients' immunosuppressive therapy. Patients were enrolled if they had severe diarrhoea (≥3 stools/day for ≥7 consecutive days). Patients with acute abdominal symptoms that required intervention within 48 hours of enrolment were excluded from the analysis.

A stepwise approach was adopted to search for infections and morphological abnormalities of the gastrointestinal tract. The severity of diarrhoea experienced by patients was confirmed by weight loss and increased serum creatinine levels. Diarrhoea was resolved as follows (the percentage figure denotes the proportion of the total patient population in which diarrhoea remission was achieved):

- Step 1 – Stop non-immunosuppressive drugs associated with diarrhoea (6%)
- Step 2 – Microbiological stool examination and treatment of bacterial infection (16%)
- Step 3 – Exclude cytomegalovirus (CMV) infection (5%)
- Step 4 – Exclude bacterial overgrowth (12%)
- Step 5 – Adaptation of immunosuppressive (IS) therapy without diagnosis (23%)
- Step 6 – Colonoscopy and adjustment of IS therapy in patients with inflammatory lesions (12%)
- Step 7 – Empirical treatment (10%)

Diagnosis or remission could not be achieved in 16% of patients. However, complete remission of diarrhoea was achieved in approximately 40% of patients without changing their immunosuppressive therapy.

Drug Reductions/Discontinuations During Study

Drug	Patients receiving drug	Patients with dose reduced/ stopped (% of total)	Dose reduced (% of total)	Dose stopped (% of total)	Remission of diarrhea (% of dose reduced/ stopped)
Mycophenolate Mofetil	96	34 (35)	23 (24)	11 (11)	22 (65)
Tacrolimus	70	12 (17)	7 (10)	5 (7)	5 (42)
Steroids	82	10 (12)	5 (6)	5 (6)	6 (60)
Cyclosporine	26	3 (12)	3 (12)	0 (0)	3 (100)

"The aetiology of severe diarrhoea following transplantation is complex and can occur many months post-transplantation. As diarrhoea is less life-threatening than the loss of a graft, the management of diarrhoea should be restrained until it becomes severe and prolonged. At this point, an aetiology should be sought so that specific and appropriately targeted treatment can be given.

"Approximately 40% of these patients, presenting with prolonged diarrhoea, may experience resolution of their diarrhoea without the need for changes in their immunosuppressive therapy. Treatments, such as the stopping of non-immunosuppressive diarrhoea-causing drugs, administration of anti-infectives, and changes in diet and lifestyle, should be considered first."

B. D. Maes

Mini-Oral Session – Kidney Immunosuppression

Apomygre:

Concentration-controlled versus fixed-dose MMF in kidney transplant recipients

A controlled-concentration MMF regimen can reduce the incidence of acute rejection

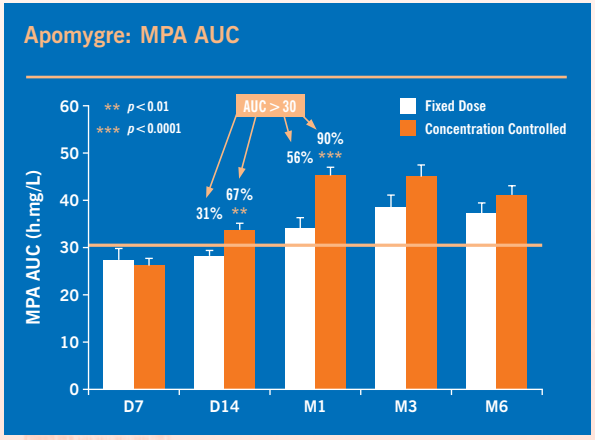
Yann Le Meur [CLICK ON NAME FOR ABSTRACT], ***University Hospital, Limoges, France*** **presented a randomised, multicentre study involving 137 renal transplant recipients.**

The study objective was to elucidate whether therapeutic drug monitoring for mycophenolate mofetil (MMF) was feasible, safe, and/or useful.

Patients were randomised into two groups: concentration-controlled and fixed-dose. The concentration-controlled group (CC; n = 70) received an initial MMF dose of 2 g/day. In this group, MPA AUC was estimated and the MMF dose adapted accordingly (target $AUC_{0\text{-}12hrs}$ = 40 mg.h/L). The fixed-dose group (FD; n = 67) were administered with an MMF dose of 2 g/day. This dose was modified on a clinical basis only. MPA AUC was estimated but not communicated to the physician.

Mean AUCs were significantly higher in the CC group on day 14 and month 1 (34 vs 27; $p < 0.01$ and 45 vs 34; $p < 0.001$ respectively). This was achieved by increasing the daily MMF dose to reach the pre-defined target (2.7 g at day 14; 2.9 g at month 1).

At six months, MPA AUCs and daily MMF doses were similar in both groups. However, compared to the CC group, biopsy-proven acute rejection and clinical rejection were higher in the FD group ($p = 0.02$ and $p = 0.04$ respectively). There were no significant differences in the incidence of gastro-intestinal (GI) effects, anaemia, or leukopaenia. The incidence of cytomegalovirus (CMV) and bacterial infections were also similar across both groups.



"Therapeutic dose monitoring for MMF using a Bayesian estimator is feasible and safe in renal transplant patients. In our study, this approach evoked less rejection with no increase of infection or GI and haematological side effects.

"Our next six-monthly follow-up will investigate whether the concentration-controlled MMF regimen leads to improved tolerability and/or whether this approach leads to fewer withdrawals or dose reductions."

Y. Le Meur

Concurrent Session – Liver: Hepatitis

One-year follow-up of HCV-3 study

Steroid-free immunosuppression in liver transplant recipients with hepatitis C may have safety and tolerability benefits

Goran Klintmalm [CLICK ON NAME FOR ABSTRACT], *Baylor University Medical Center, Dallas, Texas, USA* presented a prospective, open-label, multicentre study involving 312 orthotopic liver transplant recipients with hepatitis C (HCV-OLT).

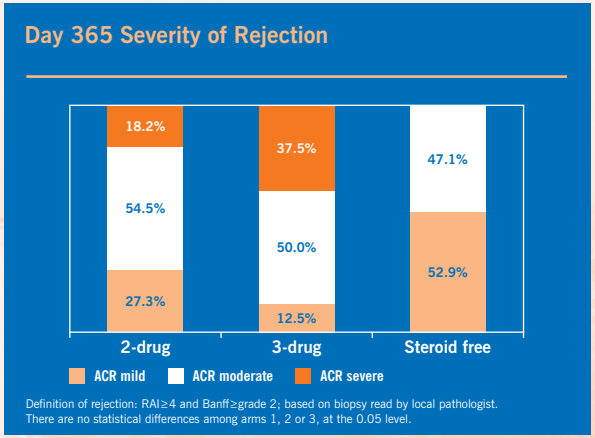
The study objective was to assess the efficacy and safety of mycophenolate mofetil (MMF) and steroid-free immunosuppression in an attempt to minimise the incidence of post-transplant acute cellular rejection (ACR), hepatitis C recurrence (HCVR), and adverse events (AE).

Patients were randomised to receive one of three immunosuppressive regimens:

- Arm 1 – tacrolimus 0.08-0.12 mg/kg/day (TAC) + prednisolone 500-1000 MP i.o. (Pred)
- Arm 2 – MMF (2-3 g/day) + TAC + Pred
- Arm 3 – MMF + TAC + three-dose daclizumab (2 mg/kg on days 0 and 3, 1 mg/kg on day 8)

Primary endpoints were clinically significant ACR (Banff grade 2 + RAI 4) and/or clinically significant HCVR (fibrosis stage ≥2 at days 90 or 365 and/or ≥3 at 730 days).

Patient and graft survival rates were similar in the three study arms. There was no statistical difference in the incidence of acute rejection or HCV recurrence, but less severe rejection was reported in the steroid-free arm. These patients also reported a numerically lower incidence of diabetes mellitus.



"Our study shows that steroid-free immunosuppression with daclizumab induction is safe and effective in hepatitis C patients. The differences in liver function at 365 days in the three study arms may reflect the impact of immunosuppression on hepatitis C. However, a longer follow-up period is required to confirm this.

"It is too early to define a role for MMF in patients with hepatitis C. Similarly, the role of steroids in hepatitis C recurrence is also unclear. However, the completion of this trial will help to support any definitive analysis or conclusions."

G. Klintmalm

Concurrent Session – Liver: Hepatitis

Hepatitis C quasispecies behaviour after liver transplantation: preliminary report from the hepatitis C III trial

Hepatitis C (HCV) recurrence may be affected by the choice of immunosuppressive regimen

Juan Gallegos-Orozco [CLICK ON NAME FOR ABSTRACT], *Mayo Clinic, Scottsdale, Arizona, USA* presented a multicentre, randomised study involving 312 liver recipients transplanted for hepatitis C (HCV) related disease.

The study objective was to assess whether HCV quasispecies behaviour after liver transplantation is influenced by the immunosuppressive (IS) regimen and/or can predict histological outcome.

Patients were randomised to receive either:

- Mycophenolate mofetil (MMF) + daclizumab + tacrolimus (TAC)

or

- MMF + prednisolone +/– TAC

Sixty-nine patients fulfilled the inclusion criteria of having pre-transplant + three-month serum samples available and a minimum three-months of follow-up data. The HVR1 region of the HCV E2 gene was amplified by RT-PCR. Quasispecies were analysed by single-strand conformation polymorphism (SSCP). Viral complexity was defined as the number of bands on the SSCP gel, and the quasispecies pattern before and 90 days following liver transplantation was correlated with protocol liver biopsy results at 3 and 12 months. Hepatitis C recurrence was defined as inflammation grade ≥3 and/or fibrosis stage ≥2 according to the Batts-Ludwig scoring system.

HCV recurrence was present in 16% of patients at the 90-day biopsy and in 69% of patients at twelve months. Recurrence rates were similar in both groups. After 90 days, compared to the steroid-containing cohort, a higher proportion of the steroid-free group reported an increase in the number of SSCP bands (35% versus 26%) and a significantly higher proportion reported a change in SSCP band pattern (59% versus 34%; p = 0.04). This change in complexity correlated with histological outcome (p = 0.01).

Quasispecies Behaviour

Comparison between pre-LT and 3-month samples

	Steroid-free group (n = 34)	Steroid group (n = 35)
Change in band pattern on SSCP	20 (59%)*	12 (34%)
Increase in number of bands on SSCP	12 (35%)	9 (26%)

*P = 0.04 (Chi square) when comparing frequency of change in band pattern in the steroid-free vs. the steroid group.

"This report provides preliminary data from the currently largest prospective trial to address the impact of immunosuppressive therapy on HCV recurrence. The study shows that the use of a steroid-free regimen leads to greater viral diversity.

"While we wait to evaluate the histological meaning of this observation, a potential explanation can be proposed: the MMF + daclizumab + TAC regimen allows more effective immune function and this is reflected by a wider viral repertoire."

J. Gallegos-Orozco

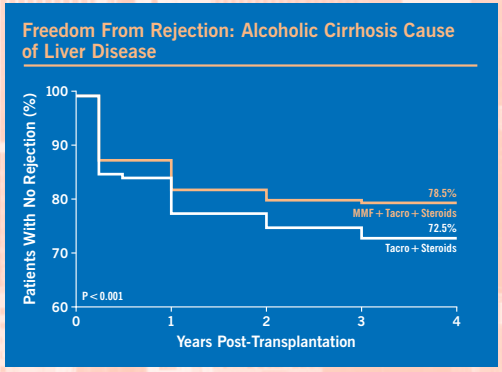
Concurrent Session – Immunosuppression/Rejection: Liver Transplantation II

Recipient risk factors predict rejection risk in liver transplant recipients

The addition of MMF to a tacrolimus and steroid immunosuppressive regimen reduces rejection risk

Russell Wiesner [CLICK ON NAME FOR ABSTRACT], *Mayo Clinic, Rochester, Minnesota, USA* presented a retrospective study using registry data from 19,279 liver transplant recipients. The study objective was to identify clinical risk factors associated with rejection.

All patients received either mycophenolate mofetil (MMF) + tacrolimus + steroids (n = 9,180) or tacrolimus + steroids (n = 10,099). Twelve covariates were used for analysis including recipient age, recipient race, cytomegalovirus (CMV) status, and donor age and gender.



"Compared to recipients with cholestatic disease, recipients with hepatitis C, hepatitis B, alcoholic cirrhosis, non-cholestatic disease, or non-viral disease have a decreased risk of rejection. In addition, our analysis showed that older recipient age is associated with a decreased risk of rejection, whilst being an African American recipient increases the risk of rejection.

"The addition of MMF to a tacrolimus + steroid regimen decreases the risk of rejection compared to tacrolimus and steroids alone. In patients with alcoholic cirrhosis and non-cholestatic disease, this reduced risk becomes significant. These data may be useful in assisting the design of patient-specific immunosuppression."

R. Wiesner

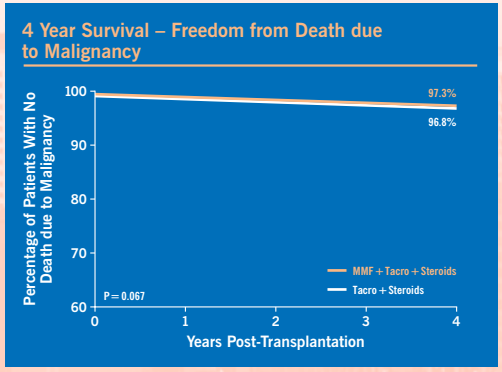
Concurrent Session – Liver Transplantation: Complications

Are triple- or dual-therapy immunosuppression regimens associated with an increased incidence of malignancy?

The addition of MMF to a tacrolimus and steroid immunosuppressive regimen is not associated with an increased incidence of fatal malignancies

John Lake [CLICK ON NAME FOR ABSTRACT], *University of Minnesota, Minneapolis, Minnesota, USA* presented a further analysis from this group of registry patients (n = 19,279).

The objective of the analysis was to determine whether the three-drug regimen of MMF + tacrolimus + steroids was associated with a higher or lower incidence of fatal and non-fatal malignancies, compared to a regimen of tacrolimus + steroids alone.



"The addition of MMF to maintenance immunosuppression that includes tacrolimus and corticosteroids does not increase the risk of death due to malignant complications.

"Conversely, pre-transplant characteristics do have a significant impact on the development of post-transplant malignancy."

John Lake

Concurrent Session – Immunosuppression/Rejection: Liver Transplantation II

Association of immunosuppressive regimens with post-liver-transplant de novo malignancies

Compared to other discharge therapies, MMF + tacrolimus reduces the risk of *de novo* malignancy

Wida Cherikh [CLICK ON NAME FOR ABSTRACT], ***UNOS, Richmond, Virginia, USA*** presented a retrospective study using OPTN/UNOS registry data from 18,404 liver transplant recipients.

The study objective was to examine the association of induction therapy and discharge maintenance immunosuppression with *de novo* cancers including skin, solid, and post-transplant lymphoproliferative disease (PTLD).

Induction therapy was classified as IL-2 receptor antibody, monoclonal antilymphocyte, polyclonal antilymphocyte, or none. All patients received discharge maintenance immunosuppression comprising:

- Mycophenolate mofetil (MMF)

or

- Azathioprine (AZA)

with or without

- Cyclosporine (CYA)

or

- Tacrolimus (TAC).

Multivariate Cox regression models were used to determine the association of induction and discharge maintenance immunosuppression on time to *de novo* malignancy, skin cancer, solid cancer, and PTLD.

None of the induction or discharge therapies had a significant association with the risk of developing *de novo* cancer. Similarly, none of the induction or discharge therapies were significantly associated with PTLD within 730 days.

Actual Incidence of *De Novo* Malignancy Within 730 Days by Discharge Regimen

Discharge Regimen	Number of TXs	*De Novo* Malignancy Incidence	
		N	%
CYA	1,941	61	3.14%
TAC	7,661	178	2.32%
CYA+AZA	855	40	4.68%
TAC+AZA	606	20	3.30%
MMF+CYA	1,371	41	2.99%
MMF+TAC	5,970	136	2.28%
All	18,404	476	2.59%

Note: P-value from chi-square test to compare cancer rates among discharge regimens was 0.0002.

"In terms of discharge maintenance therapies, our study shows that MMF + TAC is associated with a significantly reduced risk of developing any de novo malignancy and skin cancer. Similarly, the use of TAC alone also reduces this risk."

W. Cherikh

Poster Session – Liver Immunosuppression: Acute/Chronic Rejection

CellCept mycophenolate mofetil
Proven Protection for the Long Term

Low tacrolimus exposure in combination with MMF is safe and effective compared to standard tacrolimus exposure following liver transplantation

MMF + low-dose tacrolimus is safe and effective, and compares favourably to MMF + standard dose tacrolimus

Paul Marotta [CLICK ON NAME FOR ABSTRACT], *University Hospital, London, Canada* presented the first correspondence from an open-label, randomised, multicentre, parallel trial involving 60 recipients of a first hepatic transplant.

The objective of this part of the study was to assess preliminary data on the efficacy, safety, and tolerability of mycophenolate mofetil (MMF) in combination with tacrolimus (TRL) over a 26- and 52-week period.

Patients were randomised to receive standard (target trough: 10-15 ng/ml; group A; n=31) or reduced (5-8 ng/ml, group B; n=29) tacrolimus in combination with MMF (median dose 2 g/day) and corticosteroids. The primary efficacy end-point was the incidence of graft loss or, biopsy-proven acute rejection (BPAR), requiring treatment with pulse immunosuppression therapy by week 26. Reports of adverse events and opportunistic infections were collected throughout the study.

Proportion of Patients Experiencing Biopsy-Proven Acute Rejection (BPAR) Requiring Treatment, or Graft Loss, by End of Week 26

	Group A (n=29)	Group B (n=29)
Patients with BPAR requiring treatment or with graft loss*	17.2% (5)	25.9% (7)
BPAR	17.2% (5)	18.5% (5)
Mild	10.3% (3)	3.7% (1)
Moderate	6.9% (2)	11.1% (3)
Severe	0.0% (0)	3.7% (1)
Graft loss	3.4% (1)	7.4% (2)
Death	3.4% (1)	7.4% (2)
Retransplantation	0.0% (0)	0.0% (0)

*One patient in Group A had BPAR followed by graft loss.

"It appears that the safety and efficacy profiles are similar in liver recipients targeted with a combination of MMF plus either standard or reduced levels of TRL. These data are in concordance with previous studies using the MMF and TRL combination in liver transplant recipients, where acute rejection rates at one year were 26%, 32%, and 16% respectively.

"The data from this trial support the use of a combination of MMF and TRL in liver transplant recipients, and suggest that reduced-dose TRL could be used."

P. Marotta

Poster Session – Liver Immunosuppression: Acute/Chronic Rejection

CellCept mycophenolate mofetil
Proven Protection for the Long Term

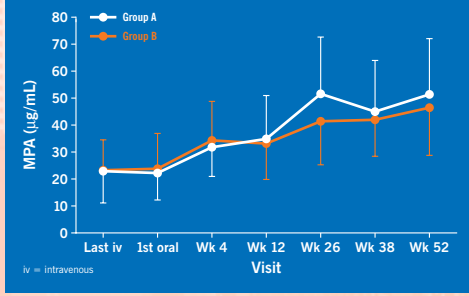
Phase II exploratory study of pharmacokinetic interactions between MMF and tacrolimus in liver transplant recipients

No pharmacokinetic interaction exists between mycophenolate mofetil (MMF) and tacrolimus in liver transplant recipients

Rene Bouw [CLICK ON NAME FOR ABSTRACT], *Roche, Welwyn Garden City, UK* presented the second part of an open-label, randomised, multicentre, parallel trial involving 60 recipients of a first hepatic transplant.

The objective of this part of the study was to characterise the pharmacokinetics of mycophenolic acid (MPA) (median dose 2 g/day) and its glucuronide metabolite (MPAG) in the presence of standard (target trough: 10-15 ng/ml; group A) or reduced (5-8 ng/ml, group B) tacrolimus (TRL) over a 52-week period.

Mean Mycophenolate (MPA) Area Under the Curve Over the Course of the Study



"In our study, MPA exposure (AUC) was not affected by exposure to TRL. This confirms findings of prior studies that no interaction occurs between MPA and TRL. Exposure to MPA after MMF dosing was in a range that has been shown previously to be well tolerated."

R. Bouw

Roche

Concurrent Session – Calcineurin Minimisation/Avoidance

CAESAR – 18 month follow-up: A comparison of low- and standard-dose cyclosporine A containing immunosuppression regimens in renal allograft recipients

Mycophenolate mofetil (MMF) in combination with daclizumab and low-dose cyclosporine A (CsA) is safe and effective and can optimise renal function

Flavio Vincenti [CLICK ON NAME FOR ABSTRACT], *UCSF, San Francisco, California, USA* presented an 18-month follow-up of a 12-month, open-label, multicentre study involving 356 *de novo* renal transplant recipients.

The study objective was to improve renal function by reducing, or withdrawing, cyclosporine A (CsA).

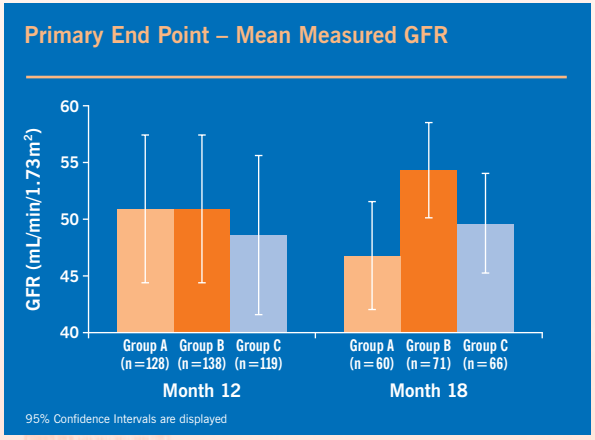
Patients were randomised to one of three groups:

- *Group A* – mycophenolate (MMF) + daclizumab (Dac), corticosteroids (CS) + low-dose CsA followed by weaning (month four) and withdrawal (month six)
- *Group B* – MMF + Dac + CS + low-dose CsA
- *Group C* – MMF + CS + standard-dose CsA.

At eighteen months, group B (low-dose CsA) patients had:

- Improved measured glomerular filtration rates (GFRs)
- Slightly higher mean measured GFRs and calculated creatinine clearances than group A (CsA withdrawal) and group C (standard dose CsA)
- Lower rates of BPAR than group A and comparable rates to group C
- Excellent patient and graft survival.

The incidence of serious adverse events was similar amongst the three groups. CMV incidence was 8% in group A, 3% in group B, and 4% in group C. The incidence of malignancies was 2%, 5%, and 1% respectively.



"Low-dose CsA with MMF, steroids, and daclizumab induction is clinically safe and effective. This regimen is similar to regimens containing standard-dose CsA in preventing early or late acute rejection."

F. Vincenti

Concurrent Session – Calcineurin Minimisation/Avoidance

Monitoring mycophenolic acid to optimise MMF therapy: what to measure and how often

MPA monitoring can optimise MMF therapy

Reinier van Hest [CLICK ON NAME FOR ABSTRACT], *Erasmus MC, Rotterdam, Netherlands* presented a retrospective data analysis of 45 renal transplant recipients.

The aims of the study were to determine whether the within-patient variability (WPV) of mycophenolic acid (MPA) exposure, in patients receiving MMF, hinders efficient therapeutic dose monitoring, and establish an optimal frequency for monitoring MPA exposure.

For each patient, MPA AUC and pre-dose concentration values (C_0) were measured on post-transplant days 3, 7, 11, 21, and months 1, 2, 3, 4, and 5. On the basis of these results, each patient was placed into one of four quartiles. Any subsequent change in AUC or C_0 which resulted in a patient changing from one quartile to another, recorded a score. Scores of 1, 2, or 3 were recorded, for changes of 1, 2, and 3 quartiles respectively.

During these first five months, WPV was low for both AUC or C_0. The mean WPV scores (± SD) for AUC and C_0 were 4.12 ± 2.98 and 6.34 ± 2.94 respectively (max 24.0). However, in the first two months, WPV was higher for C_0 than for AUC.

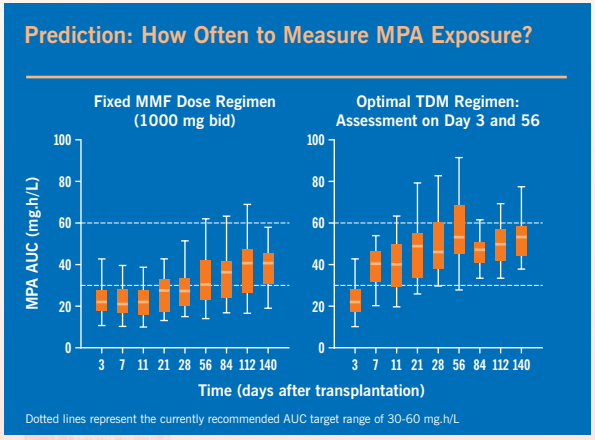
These observations, coupled with the results of several computer simulations, prompted the investigators to predict that MPA exposure could be optimised as follows:

- One assessment in the first week after transplantation to reduce between-patient variability and reach MPA exposure target levels
- One assessment to compensate for the increase of MPA exposure two months after transplantation

"Our study indicates that, with MMF within-patient variability is low, allowing an efficient therapeutic dose monitoring. MPA exposure should be measured once in week one and once after two months. Unless major changes in patient condition or co-medication occur, significant changes in MPA exposure are unlikely. However, these results need to be prospectively confirmed.

"Furthermore, whether the practice of optimising exposure will lead to fewer rejections or less toxicity remains to be established."

R. van Hest



Concurrent Session – Evolving Challenges in Transplant Infections

Prospective assessment of valganciclovir for the treatment of CMV infection and disease

Oral valganciclovir is equivalent to IV ganciclovir in patients with CMV infection and CMV disease

Atul Humar [CLICK ON NAME FOR ABSTRACT], *University of Toronto, Toronto, Canada* presented a prospective study involving 90 transplant recipients with cytomegalovirus (CMV) infection.

The study objective was to assess clinical and virologic outcomes in 31 patients treated with valganciclovir for CMV infection and CMV disease, and compare them to 52 historical controls who received IV ganciclovir.

Thirty-one patients received valganciclovir 900 mg b.d.. Doses were adjusted according to renal function. The primary endpoint was virologic clearance at 3 weeks post-start of treatment. Baseline characteristics (demographics, type of transplant, median viral load) were comparable in the two groups.

The initial analysis found that the rate of virological clearance assessed by CMV antigenaemia was similar in both groups (83.9% for valganciclovir vs 93.2% for IV ganciclovir; p = non significant). Between-group responses were also similar when the analysis was re-performed using a more sensitive PCR assay (detection limit 10-100 copies/ml) and cases were matched for transplant type and baseline viral load.

In both arms, two patients (6%) developed significant neutropoenia (<1.0 billion/L). Three additional patients in the valganciclovir group and one patient in the IV ganciclovir group developed milder neutropoenia, which necessitated dose reduction or temporary discontinuation.

Comparison of Virologic and Clinical Outcomes

Characteristic	Ganciclovir (n=32)	Valganciclovir (n=32)
Clearance of viremia by day 21 of treatment	15 (46.9%)	16 (50.0%)
Change in VL by day 7 (median $\log_{10}$ decline)	-0.64 (-3.49 to +0.98)	-0.73 (-1.94 to +1.41)
Change in VL by day 14 (median $\log_{10}$ decline)	-1.30 (-3.58 to +0.57)	-1.20 (-2.94 to +0.04)
Clinical success	32 (100%)	30 (93.8%)

"Valganciclovir is a treatment option for CMV infection and symptomatic disease in all solid organ transplant recipients. Our study shows that rates of virologic and clinical response are similar to IV ganciclovir."

A. Humar

Concurrent Session – Viruses in Transplantation

Efficacy and safety of oral valganciclovir for CMV prophylaxis in paediatric liver transplantation

Oral valganciclovir is as safe and more effective than IV ganciclovir in paediatric liver transplant recipients

I Fen Chang [CLICK ON NAME FOR ABSTRACT], *Texas Children's Hospital, Houston, Texas, USA* presented a retrospective study of all paediatric orthotopic liver transplant (OLT) recipients admitted to Texas Children's Hospital between 2001 and 2004.

The study objective was to determine whether oral valganciclovir was safe and efficacious in this group of patients for cytomegalovirus (CMV) prophylaxis.

Fifty-two patients satisfied the study inclusion criteria. Forty-one patients received oral valganciclovir (15-18 mg/kg) and the remaining eleven patients received IV ganciclovir (5 mg/kg). The treatment duration was 100 days. CMV antigenaemia was performed weekly for 100 days, monthly for one year, then as required on suspicion of CMV infection. Laboratory parameters were measured at baseline and day 100.

There were no significant inter-group differences in the incidence of CMV infection amongst high-risk patients. Greater efficacy was shown by oral valganciclovir vs IV gancliclovir; 15% of the valganciclovir group experienced CMV viraemia compared to 64% of the IV ganciclovir group ($p = 0.001$).

Although laboratory parameters were similar in both groups, 64% of patients in the IV ganciclovir group required hospitalisation (for catheter related infections) whilst no patients in the valganciclovir group were hospitalised.

Efficacy

	Low-risk no. (%) n = 33	High-risk no. (%) n = 8	p-value
CMV infection while on treatment	1 (3)	1 (12)	NS
CMV infection after treatment	1 (3)	1 (12)	NS
CMV disease after treatment	1 (3)	0	NS
Acute rejection (follow-up 12 mo. post-OLT)	4 (12)	1 (12)	NS
Rejection associated with CMV infection	1 (3)	0	NS

"Our study indicates that oral valganciclovir, at a once-daily dose of 15-18 mg/kg, is well tolerated and effective for CMV prophylaxis in paediatric OLT recipients.

"A well-designed, controlled prospective study is now warranted to confirm that this dose of valganciclovir is as effective and safe as IV ganciclovir in this paediatric patient population."

I. Fen Chang

Poster Session – Hepatitis: Liver

Zenapax daclizumab

Pharmacokinetics and pharmacodynamics of three-dose daclizumab induction

A novel three-dose daclizumab induction regimen rapidly reaches effective therapeutic levels in liver transplant recipients with hepatitis C (HCV)

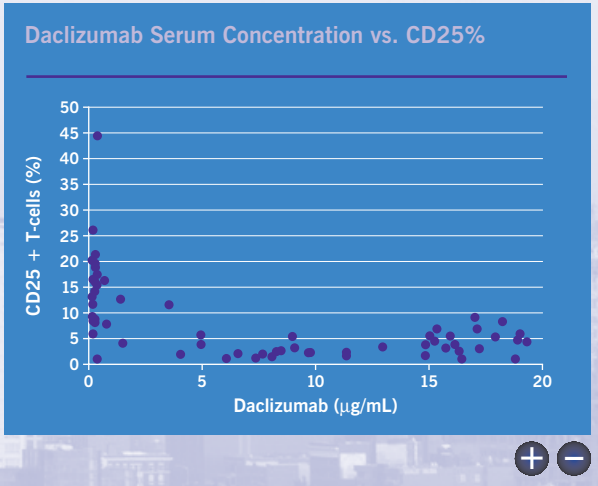
Ken Washburn [CLICK ON NAME FOR ABSTRACT], *Baylor University Medical Centre, Dallas, Texas, USA* presented a 30-patient sub-study of the Baylor HCV Liver Clinical Trial.

The aim of the study was to evaluate the pharmacokinetics and pharmacodynamics of a novel three-dose regimen of daclizumab in *de novo* hepatitis C liver transplant recipients.

Thirty adult primary liver transplant recipients with end-stage liver disease from hepatitis C were enrolled into the sub-study. All patients were treated with combination immunosuppression therapy comprising daclizumab, mycophenolate mofetil, and tacrolimus. Daclizumab was administered intravenously on post-transplant days 1, 3, and 8 at doses of 2 mg/kg, 2 mg/kg, and 1 mg/kg respectively.

Daclizumab blood samples (trough and peak on days 1, 3, and 8, and trough on day 30) were collected and analysed. Serum concentration and CD25% lymphocyte subset levels were recorded.

On day one, the mean serum concentration of daclizumab rose rapidly to an effective therapeutic level (503 μg/mL). There was also a rapid and significant decline in mean CD25% lymphocyte subset (15.7% to 4.7%). Mean trough levels remained at therapeutic levels on days 3 and 8 (21.8 μg/mL, 25.7 μg/mL), and on day 30, an effective level was maintained (9.9 μg/mL). Very low CD25% lymphocyte subsets were observed throughout the study period, with levels reaching 2.8% by day 30. Elevated baseline CD25% lymphocyte subset levels were observed in both African American patients weighing ≤75kg and patients younger than 60 years of age.



"Over a 30-day treatment period, the novel three-dose daclizumab regimen used in this study is very effective at achieving both high therapeutic drug concentrations and a significant decline in CD25% lymphocytes. We have now shown that this dose regimen is successful in a population of liver transplant recipients with hepatitis C."

K. Washburn

Roche

[1513] *MMF SUBSITUTION FOR CSA IN CHRONIC ALLOGRAFT DYSFUNCTION: 2 YEAR FOLLOW-UP OF A MULTI-CENTER RANDOMIZED CONTROLLED STUDY*

Christopher Dudley, Erich Pohanka, Hany Riad, Jarmila Dedochova, Peter Wijngaard, Sharon Marshall, Helio Tedesco Silva. Richard Bright Renal Unit, Southmead Hospital, North Bristol NHS Trust, Bristol, United Kingdom; Department of Nephrology and Dialysis, Clinic for Internal Medicine, University of Vienna Medical School, Vienna, Austria; Renal Transplant Unit, Manchester Royal Infirmary, Manchester, United Kingdom; Internal Clinic FNsP, Ostrava-Poruba, Czech Republic; Pharmaceuticals Division, F. Hoffman-La Roche Ltd, Basel, Switzerland; Hospital de Hipertensao e do Rim, Universidade Federal de Sao Paulo, Sao Paulo, Brazil.

The commonest cause of late graft loss after renal transplantation is chronic allograft dysfunction (CAD), characterized by a progressively increasing serum creatinine over time ('creeping creatinine').

A 143-patient multi-center randomized controlled study demonstrated the benefit to renal function of adding mycophenolate mofetil (MMF) to the immunosuppressive regimen followed by CsA withdrawal in patients with CAD. In the MMF group, renal function stabilized or improved in 58% of the patients (defined by a flat or positive slope of the reciprocal creatinine plot) compared to 32% in the CsA group ($p = 0.006$). 103 patients completed the one-year core study and were eligible to enter a 4-year, observational, follow-up study.

Interim data from 2 years of follow-up on 79 patients (41 from the MMF group, 38 from the CsA group) show that the improvement in renal function demonstrated in the core study is maintained. The difference in slopes between the CsA group and MMF group at 2 years was -0.00284 ($p = 0.022$). Analysis of renal function by study phase shows that the effect occurs early after addition of MMF and withdrawal of CsA, and is maintained over time.

The difference becomes greater in a per-protocol analysis of patients who remain CNI-free in the MMF group, and those who continue CNIs in the CsA group. There was no late acute rejection in either group. Three deaths occurred during the 2 year follow up in the MMF group (lymphoma, sepsis), and two in the CsA group (sepsis). Graft loss occurred in eleven patients, seven in the MMF group (chronic rejection, CAD) and four in the CsA group (chronic rejection, CAD).

These data are consistent with those in other recent studies , and demonstrate that the substitution of CsA with MMF in patients with a 'creeping creatinine' after renal transplantation results in improvement or stabilization of renal function that is maintained up to 2 years of follow-up.

[1648] *THE INCREASING USE OF THE RAPA/FK COMBINATION; EVIDENCE FOR WORSE RENAL ALLOGRAFT SURVIVAL*

Herwig-Ulf Meier-Kriesche, Jesse D. Schold, Shiro Fujita, Richard J. Howard, Bruce Kaplan. University of Florida, Gainesvile, FL.

Rapamycin (Rapa) potentiates calcineurin inhibitor (CI) nephrotoxicity. Prospective and retrospective studies have shown that cyclosporine (CsA) nephrotoxicity is enhanced by Rapa leading to worse renal allograft survival. Tacrolimus (FK) is perceived to be less nephrotoxic than CsA, and therefore CsA has been largely replaced by FK when CI's are used with Rapa. No data is available about the long-term clinical safety of FK/Rapa. From the latest released update of US transplant (Tx) data provided by the SRTR, sufficient follow up is now available to begin to address the question of graft survival with the combination of FK/Rapa versus the current gold standard combination of MMF/FK.

Methods: We analyzed 44,915 adult renal transplant recipients in the US from 2000 to 2004 on a discharge regimen of either FK/CsA and either MMF/Rapa. We described trends in regimen usage and generated univariate and adjusted models for overall and death censored graft survival.

Results: 3524 (7.8%) patients received a baseline regimen of FK/Rapa, which demonstrated inferior overall (Log-Rank $p < 0.001$) and death censored graft survival ($p < 0.001$) as compared to MMF/FK (see table). This effect was confirmed in multivariate Cox models; the adjusted hazard ratio for overall graft loss with FK/Rapa was 1.47 (95% C.I. = 1.32, 1.63) and for Neoral/Rapa 1.38 (95% C.I. = 1.20, 1.59) relative to MMF/FK. Six month acute rejection rates were low (11.5-12.6%) but not different between groups.

Conclusions: Since the growing concerns about the CsA/Rapa combination, there has been a significant increase in the use of FK with Rapa. National data indicate that FK/Rapa as compared to MMF/FK is associated with significantly worse graft survival in all subgroups of patients, but particularly in high risk grafts (DD, ECD and AA Tx), which might show earlier susceptibility to nephrotoxic insults. The magnitude is similar, if not bigger, than the previously described deleterious effect of CsA/Rapa.

		Overall Graft Survival		Death Censored Graft Survival	
Population	Regimen	One-year	Three-year	One-year	Three-year
DD Tx	FK/Rapa	88.5	74.5	93.1	83.6
	MMF/FK	92.7	82.8	95.9	90.4
ECD Tx	FK/Rapa	77.3	57.5	83.9	64.8
	MMF/FK	87.6	74.5	92.8	84.6
Living Tx	FK/Rapa	95.6	87.5	97.5	92.1
	MMF/FK	96.5	90.4	98.0	94.4
Caucasian	FK/Rapa	93.0	83.6	96.3	90.4
	MMF/FK	94.8	87.4	97.6	93.6
AA	FK/Rapa	88.2	72.5	92.2	80.4
	MMF/FK	92.7	81.4	95.7	87.7
All Tx	FK/Rapa	91.7	80.3	95.1	87.4
	MMF/FK	94.2	85.9	96.8	92.0

Deceased Donor (DD) Expanded Criteria Donor (ECD) African American (AA)

[155] *PROLONGED DIARRHEA IN RENAL TRANSPLANT PATIENTS: RESULTS OF THE DIDACT STUDY*

B. D. Maes, K. Hadaya, B. de Moor, P. Cambier, P. Peeters, J. de Meester, J. Donck, J. Sennesael, J.-P. Squifflet. Universitair Ziekenhuis Gasthuisberg, Leuven; ULB Erasme Brussels; Virga Jesse Ziekenhuis Hasselt; CHR la Citadelle Liège; Universitair Ziekenhuis Gent; Onze-Lieve-Vrouw Ziekenhuis Aalst; Academisch Ziekenhuis Sint-Lucas Gent; Universitair Ziekenhuis VUB Brussel; Cliniques Universitaires Saint-Luc Brussel, Belgium.

Diarrhea is commonly reported as adverse event in solid organ transplant patients and, if persistent, may be linked with graft loss. DIDACT – Diarrhea Diagnosis Aid and Clinical Treatment – is a prospective study in renal transplant patients developing diarrhea, defined as having ≥ 3 stools per day during a period of ≥ 1 week.

A stepwise approach was applied to search for infections and morphological abnormalities of the gastrointestinal tract (from non-invasive to invasive) and to document changes in immunosuppressive (IS) therapy. 108 patients on various IS regimens were enrolled in 9 centers with a stool frequency of 5 (range 3-15) per day during 20 (range 7-100) days.

In 6.5% diarrhea resolved after stopping concomitant non-IS drugs. In 40.7% an infectious cause was documented with resolution of diarrhea in 80% of them. Changing IS therapy without diagnosis resulted in remission (i.e. < 3 stools per day) in another 23.1%. Of patients with inflammatory lesions on colonic biopsy, 13/17 (12%) cured after adjustment of IS therapy. Of the remaining 20 patients, 11 had alleviation of symptoms by using antidiarrheal drugs or flora regulators. In the end, in only 17 (15.7%) patients no diagnosis or remission of the diarrhea was obtained.

These data suggest that infections are a major contributor to the development of diarrhea episodes after renal transplantation (more than 40%) and should be searched for thoroughly and treated prior to changing IS therapy. After exclusion of infections, modifying IS therapy resulted in remission in two thirds of the patients. Results of those changes did not seem to be linked to any specific IS drug, but rather to the level of IS in general. The remaining patients were treated symptomatically.

[338] *CONCENTRATION CONTROLED VERSUS FIXED DOSE OF MMF IN KIDNEY TRANSPLANT RECIPIENTS: PRELIMINARY RESULTS OF A FRENCH MULTICENTER RANDOMIZED STUDY*

Yann Le Meur, Matthias Büchler, Sylvie Lavaud, Isabelle Etienne, Pierre-François Westeel, Antoine Thierry, Sophie Caillard, Florence Villemain, Catherine Allard, Lionel Rostaing, Eric Thervet, Jean Christophe Szelag, Jean-Philippe Rérolle, Pierre Marquet. Department of Nephrology, University Hospital, Limoges; Tours; Reims; Rouen; Amiens; Poitiers; Strasbourg; Angers; Caen; Toulouse; Hopital Necker, Paris, France.

Accumulating data suggests that therapeutic drug monitoring (TDM) may optimize efficacy and tolerance of MMF. It could guarantee better exposure to the drug in the first 3 months and then minimize side effects in the long term. However definitive proof is still lacking.

Methods: We conducted a randomized study in 11 French centres and included 137 kidney transplant recipients (PRA < 50%) receiving a classical immunosuppressant regimen with basiliximab, Csa, MMF and steroids. The 'fixed dose' group (FD, 67 patients) received 2 g of MMF a day. The 'concentration controlled' group (CC, 70 patients) received a MMF dose adapted to the area under the concentration curve (AUC) of MPA, with a target of 40 h.mg/L. After transplantation AUCs were calculated with a Bayesian estimator using a 3-point limited sampling strategy on day 7, 14, and month 1, 3, 6, 12 in both groups (values not communicated to the physicians in the FD group).

Results: Data is presented at 6 months. Mean AUCs were significantly higher in the CC group on day 14, M1 and M3 (34 vs 27, 45 vs 34 and 45 vs 37 h.mg/L; $p < 0.01$) due to an increased daily dose of MMF to reach the predefined target: 2.7g at D14, 2.9g at M1 and 2.3g at M3. At M6, MPA AUCs and daily dose of MMF were similar in both groups. Patient and graft survival rates were similar (death: 2 CC vs 2 FD, graft loss: 1 CC vs 2 FD). Biopsy proven acute rejection tended to be less in the CC group (5 vs 13, $p = 0.054$). There were no differences in terms of bacterial infections (13 CC vs 12 FD), CMV infections (9 vs 9) GI adverse events (18 vs 13) leukopenia (10 vs 11) or anaemia (35 vs 33).

Conclusion: TDM for MMF using a Bayesian estimator is feasible and safe in transplant patients and leads to an increased MMF dose up to M6. Preliminary results at 6 months showed less rejection with no increase of infections or GI and hematological side effects in the CC group. The hypothesis of a better tolerance of MMF after 6 months in the CC group has to be investigated by the follow-up of the patients up to M12.

[475] *MULTICENTER RANDOMIZED HEPATITIS C (HCV) THREE TRIAL POST LIVER TRANSPLANTATION (OLT): A ONE-YEAR FOLLOW UP REPORT*

Carlos G. Fasola, Thomas G. Heffron, Linda Sher, David D. Douglas, Robert Brown, John Ham, Lewis Teperman, Michael Hanaway, Devin Eckhoff, Ken W. Washburn, Michael Millis, John Roberts, Michael Charlton, Peter Baliga, Timothy Pruett, Baburao Koneru, Elizabeth Pomfret, Michael Abecassis, Goran B. Klintmalm. Transplantation, Baylor University Medical Center, Dallas, TX; Hepatitis C Three Group, Multicenter.

Aims: To assess the efficacy and safety of mycophenolate mofetil (MMF) and steroid (Pred)-free immunosuppression in an effort to minimize acute cellular rejection (ACR), HCV recurrence (HCVR) and adverse events (AE) post OLT.

Methods: The trial was designed as an open label, prospective, multicenter study involving 312 adult HCV-OLT recipients. Patients were randomized (1:1:2) pre-OLT to three immunosuppression regimens. Arm 1: tacrolimus (TAC) + Pred; Arm 2: TAC + Pred + MMF and, Arm 3: TAC + MMF + 3 dose daclizumab without steroids. Laboratory data and liver histology were evaluated when clinically indicated and, by protocol, at 90, 365 and 730 days. ACR was graded according to Banff criteria. HCVR was staged according to Batts and Ludwig. Primary endpoints were clinically significant ACR (Banff grade 2 + RAI 4) and/or clinically significant HCVR (fibrosis stage $\geq$2 at days 90 or 365 and/or $\geq$3 at 730 days). Statistics: $p \leq 0.05$ (Fisher and log-rank tests)

Results: Of 312, 151 patients had limited 1-year follow up data available for this preliminary analysis. There were no statistical differences for most parameters studied. Respectively, graft survivals in arms I, II and III were: 90%, 97% and 95% and, patient survivals: 95%, 97% and 96%. Two patients died in arm I (respiratory malignancy, renal failure); 1 in arm II (respiratory infection) and, 3 in arm III (cardiac, respiratory infections). Significant ACR was present, respectively, in 16%, 9% and 5%. HCVR incidences showed no differences across arms (I: 30%; II:49% and III:35%) and, no differences were found, either, regarding the incidences of infections, malignancies, hyperlipidemia and diabetes.

Conclusions: This one-year preliminary report suggests the safety of the Pred-free immunosuppression (TAC + MMF + daclizumab) used in the trial. The low ACR rate in arms 2 and 3 is encouraging, since most ACR occur during the first year post OLT. All patients will have completed 1-year follow up and available results will be reported at the meeting.

[482] *HEPATITIS C HYPERVARIABLE REGION 1 QUASISPECIES BEHAVIOR AFTER LIVER TRANSPLANTATION: A PRELIMINARY REPORT FROM THE HEPATITIS C III TRIAL*

Juan F. Gallegos-Orozco, Hugo E. Vargas, Devin E. Eckhoff, Hepatitis C III Study Group. Division of Transplantation Medicine, Mayo Clinic Scottsdale, Scottsdale, AZ; Department of Surgery, University of Alabama at Birmingham, Birmingham, AL.

Purpose: Hepatitis C III Trial is a multicenter, randomized study to assess safety and efficacy of a steroid-free immunosuppressive (IS) protocol (daclizumab, tacrolimus and MMF) in patients transplanted for HCV-related disease. We hypothesize that HCV quasispecies behavior after liver transplantation (LT) is influenced by the IS regimen and can predict histological outcome.

Methods: Patients with minimum 90-day follow-up and available pre-LT and 90-day serum samples were studied. Hypervariable region 1 of the HCV E2 region was amplified by RT-PCR. HCV quasispecies were analyzed by single strand conformational polymorphism (SSCP), which can detect a single nucleotide difference between sequences and $\geq$3% minor variant admixture. Viral complexity was defined as the number of bands on SSCP gels. Quasispecies pattern before and 90 days after LT were correlated to liver biopsy. HCV recurrence was defined as inflammation grade $\geq$3 and/or fibrosis stage $\geq$2 (Batts-Ludwig score).

Results: A total of 312 patients were enrolled into the trial. SSCP analysis has so far been performed in 51 patients (28 in the steroid-free group). Day 90 and 1-year protocol liver biopsies were available in 44 and 29 patients, respectively. Recurrence was present in 7 patients (16%) at 90-day biopsy and in 20 patients (69%) at 1-year biopsy. Rates of recurrence were not significantly different in the steroid-free and steroid-treated groups: 12.5% vs. 20% at 90 days and 75% vs. 62% at 1 year ($p = 0.7$). A *shift* in SSCP band pattern from pre-LT to 90-day sample, reflective of sequence changes, was seen in 30 patients. Its occurrence was significantly more frequent in the steroid-free group (71% vs. 43%, $p < 0.05$). Viral *complexity change* from pre-LT to day-90 sample correlated with outcome: significant fibrosis (stage $\geq$2 at 1-year biopsy) was present in 36% of patients with *increased viral complexity* compared to 83% of patients with *stable* or *decreasing complexity* ($p = 0.01$, likelihood ratio 6.7).

Conclusions: This report provides preliminary data from the currently largest prospective trial addressing the impact of IS on HCV recurrence. Early variations in HCV quasispecies *complexity* on SSCP may predict 1-year outcome with regard to severity of HCV histological recurrence, and may be affected by the administered IS regimen.

[928] *RECIPIENT RISK FACTORS PREDICT RISK OF REJECTION IN ADULT LIVER TRANSPLANT RECIPIENTS*

Russell Wiesner, Kristin David, Bettina Steffen, Joachim Schupp, Robert Gordon, John Lake. Liver Transplant Center, Mayo Clinic, Rochester, MN; ProSanos Corporation, La Jola, CA; Roche Laboratories, Nutley, NJ; Division of Gastroenterology, University of Minnesota, Minneapolis, MN.

Methods: To investigate factors affecting rejection, data from adult (18-80 yrs) primary liver transplant recipients recorded on 3-drug (MMF/Tacro/CS) (n = 9,180) or 2-drug (Tacro/CS) (n = 10,099) therapy were analyzed. Data were from the SRTR and included patients transplanted between June 1995 and April 2004.

Results: Kaplan-Meier analysis showed significantly lower rejection rates 4-year post transplant in 3- vs. 2-drug patients (25.6% vs. 30.1%, $p<0.001$). Cox proportional hazards regression confirmed 3- vs. 2-drug therapy to be associated with a decreased risk of rejection (HR: 0.92, $p=0.007$). Cause of underlying liver disease was also associated with risk of rejection: compared to cholestatic disease, patients with HBV (HR: 0.68, $p<0.001$), alcoholic cirrhosis (HR: 0.74, $p<0.001$), HCV (HR: 0.86, $p<0.001$), and non-cholestatic/non-viral liver disease (HR: 0.86, $p=0.004$) had a decreased risk. Recipients undergoing transplantation because of malignancy were not at increased risk for rejection. Other variables associated with a decreased risk of rejection included: year of transplant and older recipient age; African American race was associated with an increased risk of rejection (table).

Conclusion: Compared to cholestatic disease, patients with HCV, HBV, alcoholic cirrhosis and non-cholestatic/non-viral liver disease had a decreased risk for rejection. The addition of MMF to tacrolimus-based immunosuppression was also associated with a decreased risk of rejection. These results may assist in the design of patient-specific immunosuppression regimens.

Selected Protective & Risk Factors from Multivariable Model Examining Relationship Between 3- vs. 2-Drug Therapy & Risk of Rejection

Variable (Reference)	HR	p
3-Drug (2-Drug)	0.92	0.007
Cause of liver disease (cholestatic)		
Non-cholestatic/Non-viral cirrhosis	0.86	0.004
HCV	0.86	<.001
Alcoholic cirrhosis	0.74	<.001
Malignancy	0.84	0.215
HBV	0.68	<.001
African American	1.29	<.001
Recipient age in decade	0.92	<.001
Transplant yr (1995-1996)	0.90	<.001

Adjusted for: Medical status, serum creatinine level, diabetes status, donor gender & age, cold ischemia time, CMV recipient status, donor & recipient HCC status

[1545] *IS TRIPLE VS. DUAL DRUG THERAPY ASSOCIATED WITH INCREASED RISK OF DEATH DUE TO MALIGNANCY IN ADULT LIVER TRANSPLANT RECIPIENTS?*

John R. Lake, Kristin M. David, Bettina J. Steffen, Joachim H. P. Shupp, Alice Chu, Jonathan A. Morris, Robert D. Gordon, Russell H. Wiesner. Division of Gastroenterology, Liver Transplant Program, University of Minnesota, Minneapolis, MN; ProSanos Corporation, La Jolla, CA; Medical Affairs, Roche Laboratories, Nutley, NJ; Liver Transplant Center, Mayo Clinic, Rochester, MN.

Objectives: Immunosuppression is often incriminated for the increased risk of post-transplant malignancies. To examine whether 3- (MMF/Tacro/CS) vs. 2-drug therapy (Tacro/CS) is associated with an increased risk for death due to malignancies, data from a large registry of primary liver transplant recipients were analyzed.

Methods: Data from adult primary liver transplant recipients reported to the SRTR between June 1, 1995 and April 30, 2004 and recorded at hospital discharge on 3-drug (n = 9,180) or 2-drug (n = 10,099) therapy were included.

Results: Kaplan-Meier survival analysis showed no significant differences in death due to malignancies 4-years post-transplantation between the 3- and 2-drug groups. Multivariable analysis using Cox proportional hazard models confirmed no differences in risk of death due to malignancy between the 3 and 2-drug groups (HR: 0.83, $p=0.113$). Incidence of any (not just those resulting in death) post-transplant malignancies, including *de novo* lymphoproliferative tumors, was also not significantly different between the 3- and 2-drug patients. These results suggest that the addition of MMF to a 2-drug regimen of tacrolimus and steroids is not associated with increased risk of death due to, or incidence of, malignancies.

Results from multivariable analysis of the relationship between 3- vs. 2-drug therapy and selected covariates for the risk of death due to malignancy

Variable (Reference)	HR	p
3-Drug (2-Drug)	0.83	0.11
Cause of Liver Disease (non-cholestatic/non-viral)		
Malignancy	18.4	<.001
Alcoholic cirrhosis	3.1	<.001
HCV	2.7	<.001
Cholestatic	2.1	0.01
HBV	1.9	0.09
Recipient age in decade	1.3	<.001

variables adjusted for each other, donor age & induction therapy

Incidence of post-transplant malignancies by 3- or 2-drug therapy

Malignancy Type	3-Drug	2-Drug	p
De Novo Lymphoproliferative	44 (0.5%)	52 (0.5%)	0.72
De Novo Solid Tumor	127 (1.4%)	171 (1.7%)	0.08
Recurrence of Pre-Transplant Tumor	91 (1.0%)	121 (1.2%)	0.17

[930] *ASSOCIATION OF DIFFERENT IMMUNOSUPPRESSIVE REGIMENS WITH POSTTRANSPLANT DE NOVO MALIGNANCIES IN LIVER RECIPIENTS*

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Aims: *De novo* malignancies are responsible for 22.1% of deaths reported to the OPTN/UNOS in liver recipients surviving for at least 5 years. Since immunosuppression is a known risk factor for post-tx *de novo* malignancies, we examined the association of induction therapy and discharge maintenance immunosuppression with *de novo* malignancies in liver recipients.

Methods: Univariate and multivariate Cox regression analyses for the development of any *de novo* malignancy, including skin, solid, and PTLD malignancies were conducted on 18,404 primary deceased donor whole liver txs during 1/1/97-12/31/02. Induction therapy was classified as IL-2 receptor antibody, monoclonal antilymphocyte, polyclonal antilymphocyte, or none. Maintenance immunosuppression was classified as cyclosporine (CYA) or tacrolimus (TAC), with or without azathioprine (AZA) or mycophenolate mofetil (MMF). Because post-transplant cancer is time dependent, records with follow-up >730 days were censored to allow comparable follow-up among drug groups. Results of the Cox analysis are presented as relative risk (RR) of cancer and p-value.

Results: Induction therapy had no significant effect on the risk of *de novo* cancer. Actual incidence of any *de novo* malignancy within 730 days was 4.68% with CYA+AZA, 2.99% with MMF+CYA, 3.30% with TAC+AZA, 2.28% with MMF+TAC, 3.14% with CYA alone, and 2.32% with TAC alone (p=0.0002). The Table shows the adjusted RR and p-value for any malignancy, skin, and non-skin solid maligancies. CYA alone was used as a reference group.

		Any Malignancy		Skin		Solid	
Drug	N	RR	P	RR	P	RR	P
CYA alone	1,941	1.00	-	1.00	-	1.00	-
TAC alone	7,661	0.680	0.012	0.221	<0.01	0.775	0.183
CYA+AZA	855	1.467	0.064	1.861	0.174	1.441	0.169
MMF+CYA	1,371	0.948	0.793	0.912	0.845	0.974	0.921
TAC+AZA	606	0.968	0.899	1.067	0.913	0.803	0.539
MMF+TAC	5,970	0.673	0.014	0.649	0.246	0.658	0.041

None of the induction or maintenance immunosuppression therapies were significantly associated with PTLD within 730 days.

Conclusions: MMF+TAC maintenance immunosuppression was associated with a significantly reduced risk of developing any malignancy and non-skin solid cancer. TAC alone was associated with a reduced risk of developing any cancer and skin cancer.

[1240] *LOW TACROLIMUS EXPOSURE IN COMBINATION WITH MYCOPHENOLATE MOFETIL IS SAFE AND EFFECTIVE COMPARED TO STANDARD TACROLIMUS EXPOSURE FOLLOWING LIVER TRANSPLANT*

Paul Marotta, Bjorn Nashan, Faouz Saliba, Francois Durand, Matthew Bowles, David Patch, Angel Bernardos, Matthew Truman, Jane Ives, Richard Mamelok. Univ Hosp, London, Canada; Dalhousie Univ, Halifax, Canada; Hopital Paul Brousse, Villejuif, France; Hopital Beaujon, Clichy, France; Kings College, London, United Kingdom; Royal Free Hospital, London, United Kingdom; Virgen Del Rocio, Sevilla, Spain; Roche, United Kingdom.

The primary aim of the study was to compare the pharmacokinetic profiles of mycophenolate mofetil (MMF) in combination with different levels of tacrolimus (TAC). Here we describe safety and efficacy data in relation to mycophenolic acid (MPA) exposure. 60 *de novo* liver transplant recipients, were randomized 1:1 to receive standard (target trough; 10-15 ng/ml, Group A) or reduced (5-8 ng/ml, Group B) tacrolimus in combination with MMF and corticosteroids (CS). CS and TAC could be tapered according to centre practice at 3 and 6 months respectively.

Patients were stratified according to HCV status. Incidental HCC was found in 17% of patients at transplant. Demographics were generally balanced; however, Group B had more patients at high risk for CMV (37% vs 20%). Both groups received a median MMF dose of 2 g/day. Median TAC levels indicate that target trough levels were constant over time and were lower in group B than A.

Overall incidence of biopsy proven acute rejection (BPAR) requiring treatment or graft loss at 6 months was low (see below). The first occurance of BPAR were all within the first 12 weeks. MPA AUC (ug.h/ml) between rejectors (n=9) vs non-rejectors (n=32), at week 1, 4, and 12 were 22.7±11.1 (SD) vs 24.8±13.6, 29.0±12.3 vs 43.9±20.5 and 45.5±18.0 vs 46.0±21.2 respectively.

ITT analysis (Month 6)	Group A (n=29)	Group B (n=27)
BPAR	17% (5)	19% (5)
BPAR or graft loss	17% (5)	26% (7)
Median calculated creatinine clearance	66.3 ml/min	78.6 ml/min

The only reason for graft loss was death, with 1 death in Group A and 2 in Group B. Adverse events of interest are presented below.

Safety analysis (Month 12)	Group A (n=29)	Group B (n=29)
Anemia	37.9% (11)	48.3% (14)
Hypertension	37.9% (11)	41.4% (12)
Diarrhea	34.5% (10)	34.5% (10)
CMV	17.0% (5)	34.5% (10)
HCV	10.3% (3)	10.3% (3)
HCC	0	3.4% (1)

It appears that safety and efficacy profiles are similar in liver recipients receiving standard or reduced levels of TAC in combination with MMF, and possibly in favour of a reduction in TAC since creatinine clearance appeared improved in this group.

[1248] *NO PHARMACOKINETIC INTERACTION BETWEEN MYCOPHENOLATE MOFETIL AND TACROLIMUS IN LIVER TRANSPLANT RECIPIENTS: A PHASE II EXPLORATORY STUDY*

Rene Bouw, Bjorn Nashan, Paul Marotta, Fauoz Saliba, J. Ignacio Herrero, Rafael Barcena, Gilles Mentha, Peter Neuhaus, Diane McKay. Roche, United Kingdom; Dalhousie Univ, Halifax, Canada; Univ Hospital, London, Canada; Hopital Paul Brousse, Villejuif, France; Clinica Univ de Navarra, Pamplona, Spain; Centro Ramon Y Cajal, Madrid, Spain; Hospital Cantonal Univ, Geneve, Switzerland; Univ Klinik Charite, Berlin, Germany.

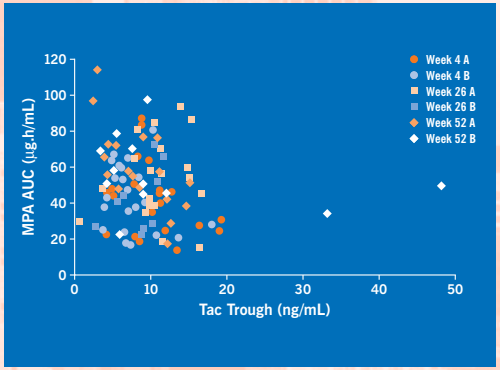
The primary aim of the study was to compare the pharmacokinetic (PK) profiles of mycophenolic acid (MPA) following administration of mycophenolate mofetil (MMF) in combination with different levels of tacrolimus (TAC). Sixty *de novo* liver transplant patients were randomized 1:1 to receive MMF (1g b.i.d) and corticosteroids in combination with either standard (target trough: 10-15 ng/mL, Group A) or reduced (5-8 ng/mL, Group B) TAC. PK profiles (0-12h) for MPA and its glucuronide (MPAG), and central trough levels for TAC were determined after the last i.v. MMF dose (i.v MMF was taken during first week post transplant), after the 1st oral MMF dose, and at weeks 4, 12, 26, 38 and 52. Fifty-five patients contributed to the PK population.

Both groups received a median daily dose of 2g MMF. Median TAC levels indicate that target trough levels were constant over time and were lower in group B than A.

Total number of patients contributing to AUC (0-12h) ranged from 18-27 in Group A and 16-25 in Group B. Exposure to MPA and MPAG was very similar between the two groups with a trend towards an increase over time (table 1). All PK results were dose-normalised to 1g MMF. MPAG results were also molecular weight adjusted to MPA equivalent. T_{max} and C_{max} were also similar between the two groups. No significant change in AUC was seen on switching from i.v. to oral MMF. No relationship between MPA AUC (0-12h) and TAC trough levels was observed.

Mean AUC 0-12 hour (ug.h/mL)(SD)					
	LAST IV	1st ORAL	Wk 4	Wk 26	Wk 52
Group A MPA	30.0(32.9)	23.9(14.5)	37.5(21.1)	46.9(21.2)	49.8(24.9)
Group B MPA	23.2(6.24)	25.1(11.9)	40.0(18.9)	40.4(18.4)	46.2(23.4)
Group A MPAG	486(291)	508(284)	507(239)	613(346)	596(232)
Group B MPAG	344(168)	376(137)	554(180)	510(195)	580(209)

In conclusion, MPA PK after MMF administration was not different in patients receiving standard or low dose TAC. Safety and efficacy data (submitted separately) were similar in both groups indicating that low dose TAC in combination with MMF appears safe and effective in liver transplant recipients.



[1507] *THE USE OF MYCOPHENOLATE MOFETIL, DACLIZUMAB AND CORTICOSTEROIDS WITH CYCLOSPORINE (LOW DOSE, LOW DOSE/ WITHDRAWAL AND STANDARD DOSE) TO OPTIMIZE RENAL FUNCTION IN RENAL ALLOGRAFT RECIPIENTS – 18 MONTH RESULTS*

Flavio Vincenti, Yves Vanrenterghem, Bjorn Nashan, Josep Grinyo, Henrik Ekberg, Clare Nasmyth-Miller, Matthew Truman, Elizabeth Calleja. UCSF, San Francisco, CA; Univ of Gasthuisberg, Leuven Belgium; Dalhousie Univ, Halifax, NS Canada; Hospital Universitari de Bellvitge, Barcelona, Spain; Univ of Lund, Malmo, Sweden; Roche, Welwyn Garden City, United Kingdom; Roche, Nutley, NJ.

356 of 536 patients consented to 18 month (mo) followup of a 12 mo open label, multicenter study designed to improve renal function in *de novo* renal transplant recipients by reduction or withdrawal of cyclosporine A (CsA). All of these patients had creatinine clearances (CrCl) calculated (Cockcroft-Gault formula) at 18 mo posttransplant, and 228 patients consented to assessment of measured glomerular filtration rates (GFR) using exogenous substrates. Patients had been randomized before transplantation in a 1:1:1 ratio to one of 3 groups. Group A patients received mycophenolate mofetil (MMF), Daclizumab (Dac), corticosteroids (CS), and low dose CsA followed by weaning (mo 4) and withdrawal (mo 6). Group B patients received MMF, Dac, CS and low dose CsA, and Group C patients received MMF, CS and standard dose CsA. Mo 12 data which fit into the mo 18 visit window contributed to this analysis.

	Group A	Group B	Group C
GFR (12 mo) mL/min/1.73 m²	50.9	50.9	48.6
GFR (18 mo) mL/min/1.73 m²	46.8	54.4	49.6
CrCl (12 mo) mL/min	67.4	71.7	66.0
CrCl (18 mo) mL/min	69.1	69.9	66.3
BPAR* (12 mo) %	38.0	25.4	27.5
BPAR* (18 mo) %	40.8	29.4	31.3

* biopsy proven acute rejection (excluding borderline)

At mo 18 posttransplant, the mean CrCls were slightly better in Groups A and B than in Group C. The mean GFR for Group B at mo 18 improved from mo 12, and was higher than that for Groups A and C, with the difference between Groups A and B being statistically significant (-7.7, 95% CI = -13.7, -1.6, p = 0.041). The incidence of first BPAR in Group B was lower than in Group A, and comparable to that of Group C at 18 mo posttransplant. The mean GFR of Group B may be higher because this group had fewer rejections than Group A and less CsA than Group C. Reported deaths and graft losses (GL) were least in Group B (4 deaths, 6 GL), compared to Group A (8 deaths, 14 GL) and Group C (6 deaths, 9 GL). Use of low dose CsA with MMF, CS, and Dac induction is clinically safe and effective for renal transplant patients through 18 mo posttransplant.

[1510] *MONITORING MYCOPHENOLIC ACID TO OPTIMIZE MYCOPHENOLATE MOFETIL THERAPY: WHAT TO MEASURE AND HOW OFTEN*

CellCept® mycophenolate mofetil
Proven Protection for the Long Term

Reinier M. van Hest, Ron A. Mathot, Arnold G. Vulto, Teun van Gelder. Clinical Pharmacology, Erasmus MC, Rotterdam, Netherlands; Internal Medicine, Erasmus MC, Rotterdam, Netherlands.

Introduction: mycophenolate mofetil (MMF) is widely used to prevent acute rejection following solid organ transplantation. Exposure to the active compound mycophenolic acid (MPA) is highly variable between patients and exposure increases with time after transplantation. In addition, MPA exposure is predictive for the development of acute rejection. Consequently, therapeutic drug monitoring (TDM) of MPA offers an attractive tool for optimization of MPA exposure. A possible limitation for efficient TDM could be a large within-patient variability (WPV) of the exposure to MPA. This study aims to analyze the extent of WPV of MPA exposure. This was done for two possible exposure parameters, area-under-the-curve (AUC) and predose concentrations (C_0).

Methods: Data from 30 renal transplant patients, who participated in a randomized concentration controlled trial, were analyzed retrospectively. AUC and C_0 values, adjusted to 1000 mg bid of MMF, for days 3, 7, 11, 21, and months 1, 2, 3, 4 and 5 after transplantation were divided into quartiles. When AUC or C_0 changed 1, 2 or 3 quartiles within a patient from one occasion to the next, a score of respectively 1, 2 or 3 points was assigned. This was done for all 8 between occasion intervals, resulting in a maximal possible score for WPV of 8 x 3 = 24 per patient. The higher the score, the more AUC or C_0 changed quartiles during the study follow-up.

Results: For C_0 the mean overall score (± standard deviation) was 5.8 of maximal 24 ± 2.6. For AUC measurements this score was 4.2 ± 2.9. The higher score for C_0 was explained by a higher WPV during the early post-transplantation time points (mean score on day 7 was 0.87 (of maximal 3) and 0.90 on day 11, while for AUC the mean scores were 0.47 and 0.53 respectively).

Conclusion: The WPV for MPA exposure is low in kidney transplant recipients during the first 5 months after transplantation. In the first weeks after transplantation WPV is larger for C_0 than for AUC. Based on this observation and on computer simulations of several TDM-based dosing regimes, the following TDM scheme may prove to be useful: one measurement of MPA exposure, preferably by AUC, in the first week after transplantation to determine the optimal MMF dose and a second measurement after 2 months to compensate for the increase in exposure with time. Unless major changes in renal function or albumin levels occur, significant changes in MPA exposure are unlikely.

[90] *PHARMACOKINETICS AND PHARMACODYNAMICS OF 3-DOSE DACLIZUMAB IN LIVER TRANSPLANT RECIPIENTS WITH HEPATITIS C*

Zenapax® daclizumab

Ken K. Washburn, Lewis W. Teperman, Thomas G. Heffron, David D. Douglas, Eli Katz, Carlos G. Fasola, Goran B. Klintmalm. Liver Transplantation, Baylor University Medical Center, Dallas, TX; Hepatitis C Three Study Group, Multicenter.

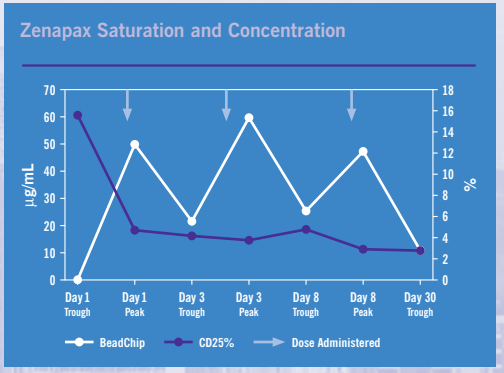
Background: Daclizumab (Zenapax, Roche Pharmaceuticals) is a highly specific humanized anti-interleukin 2 receptor (IL-2R) monoclonal antibody. Daclizumab is approved for induction therapy in renal transplant patients as a 5-dose regimen. Yet, the pharmacokinetics and pharmacodynamics of Daclizumab have not been well characterized in liver transplant recipients.

Objective: This study evaluated Daclizumab serum concentrations (pharmacokinetics) and CD25 saturation levels (pharmacodynamics) of *de novo* hepatitis C liver transplant recipients who received a novel 3-dose regimen.

Methods: Thirty patients enrolled in arm 3 of the HCV3 Liver Study, received daclizumab intravenously on post-operative days 1, 3, and 8 (2, 2, and 1 g/kg respectively), in steroid-free regimen with tacrolimus and mycophenolate mofetil. Blood samples, pre-dose (trough) and 60 minutes after infusion (peak) on Days 1, 3, and 8, and on day 30, were analyzed for serum concentration (Beadchip™ technology) and for CD25 saturation (flow cytometry).

Results: An effective therapeutic level was observed on Day 1 (mean 50.3 g/mL). Trough levels remained in the therapeutic range (mean: 21.8 and 25.7 g/mL, on Days 3 and 8 respectively) and in the effective range at Day 30 (mean: 9.9 g/mL). A rapid decline in CD25 lymphocytes (mean: 15.7% to 4.7%) on Day 1, and low level of CD25% lymphocyte through Day 30 (2.8%) were observed. A good correlation was observed between daclizumab level 5 g/ml and suppression of CD25 lymphocytes.

Conclusions: The novel dose regimen used in this study, 3 doses of daclizumab on days 1, 3, and 8 post-transplantation, is very effective in achieving high therapeutic concentrations of daclizumab and a significant decline in CD25% lymphocyte sub-sets to a very low level lasting over 30 days.



[902] *A PROSPECTIVE ASSESSMENT OF VALGANCICLOVIR FOR THE TREATMENT OF CYTOMEGALOVIRUS (CMV) INFECTION AND DISEASE IN TRANSPLANT RECIPIENTS*

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Background: Valganciclovir has good oral bioavailability and may be a more convenient alternative to intravenous ganciclovir for the treatment of CMV infection and disease. We prospectively assessed valganciclovir for the treatment of CMV infection and disease and compared virologic and clinical outcomes to historical controls.

Methods: Patients with CMV infection and symptomatic disease who met inclusion criteria were given therapeutic doses of oral valganciclovir. Historical controls were treated with intravenous ganciclovir. CMV antigenemia and viral load testing were done at regular intervals after the onset of treatment. The primary endpoint was virologic clearance at 3 weeks post-start of treatment. Viral load testing was done using a real-time lightcycler based PCR assay.

Results: A total of 90 patients were assessed. 31 transplant recipients with CMV infection (of whom 74.2% had symptomatic disease) were treated with valganciclovir either up-front (n=29) or as early step-down therapy (n=2; within 72 hours). Outcomes were compared with 59 historical controls treated with IV ganciclovir. Baseline demographics including age, sex and donor/recipient serostatus and symptom presentation were comparable in the two groups. Type of transplant included liver (n=18), lung (n=30), kidney (n=29) and other (n=13) and were similar in both groups. Median viral load at disease onset was 3.6 $\log_{10}$ copies/ml in the valganciclovir arm and 3.9 $\log_{10}$ copies/ml in the ganciclovir group (p=NS).

The rate of virologic clearance at 3 weeks post-treatment was similar in the valganciclovir group (67.7% undetectable viral load by 3-weeks; 83.9% had negative antigenemia) vs. the ganciclovir group (69.5% undetectable viral load (p=NS); 93.2% negative antigenemia (p=0.26)). 2/31 (6.5%) patients treated with valganciclovir required switch to IV ganciclovir for lack of clinical and/or virologic response to oral therapy (1 with documented UL97 mutation).

Conclusions: Valganciclovir appears to be useful for treatment of CMV infection and disease in selected patients provided close clinical and virologic follow-up are performed. Rates of virologic and clinical response were similar to IV ganciclovir.

[1586] *EFFICACY AND SAFETY OF ORAL VALGANCICLOVIR (VGC) FOR CMV PROPHYLAXIS IN PEDIATRIC ORTHOTOPIC LIVER TRANSPLANTATION (POLT)*

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Cytomegalovirus (CMV) is a major source of mortality and morbidity following POLT. Although VGC has a bioavailability that is 10-fold greater than oral ganciclovir (GCV), data supporting its use in POLT is currently lacking.

Objective: To evaluate the safety and efficacy of PO VGC vs. IV GCV for CMV prophylaxis after POLT.

Methods: Retrospective review from 1999-2004 identified 52 POLT recipients who received 100 days of IV GCV 5 mg/kg (IVG) or crushed VGC tabs 15-18 mg/kg (POG) for CMV prophylaxis. Diagnosis of CMV infection was made based on clinical symptoms and/or serological evidence of viremia detected by CMV antigen. The incidence of post-OLT CMV infection in each group was compared using Fisher's exact test. Changes in serum creatinine (SCr), white blood cell count (WBC), absolute neutrophil count (ANC), hemoglobin (Hgb) and alanine aminotransferase (ALT) seen pre-OLT and post-therapy were compared using Mann-Whitney U-test. A p-value of <0.05 was considered statistically-significant.

Results: 41 patients received PO and 11 received IV regimen with a median follow-up of 17.5 mo (range 3-32) and 42.5 mo (range 27-50), respectively. During the 100 day course, 2 patients in the POG (D+R-, D+R+) and 1 patient in the IVG (D+R+) were identified to have serological evidence of viremia (p=0.52, Fisher's exact test). However, no significant differences between groups were seen in the incidence of CMV infection among high-risk patients (p=0.20).

No significant differences were also noted in the levels of SCr, WBC, ANC, Hgb or ALT at pre-OLT and at 100 days. To date, 6 (15%) in the POG and 7 (64%) in the IVG have experienced CMV viremia after completing prophylaxis (p=0.001). Seven (64%) patients in the IVG and none in the POG required hospitalization for catheter related infections.

Conclusions: Oral VGC appears as safe and effective as IV GCV for CMV prophylaxis in POLT. Oral VGC eliminates the need for long-term central venous access and its associated complications.

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